# Weight Gain Velocity in Very Low-Birth-Weight Infants: Effects of Exposure to Biological Maternal Sounds

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**Abstract**

**Objective**   To examine the effects of biological maternal sounds (BMS) on weight gain velocity in very low-birth-weight (VLBW) infants ($\leq$ 1,500 g).

**Study Design**   An exploratory study with a matched-control design. A prospective cohort of VLBW infants exposed to attenuated recordings of BMS during their neonatal intensive care unit hospitalization were compared with retrospective controls matched 1:1 for sex, birth weight, gestational age, scores for neonatal acute physiology and perinatal extension (SNAPPE - II) scores ($n = 32$).

**Results**   A linear mixed model controlling for gestational age, chronic lung disease, and days to regain birth weight revealed that infants receiving BMS significantly improved their weight gain velocity compared matched controls ($p < 0.001$) during the neonatal period. No differences were found on days spent nothing by mouth ($p = 0.18$), days until full enteral feeds ($p = 0.51$), total fluid intake ($p = 0.93$), or caloric intake ($p = 0.73$).

**Conclusion**   Exposure to BMS may improve weight gain velocity in VLBW infants. Further research is needed to evaluate the effectiveness of this noninvasive intervention during the neonatal period.

**Keywords**
► weight gain velocity
► auditory
► neonatal
► very low birth weight

Very low-birth-weight (VLBW) infants ($\leq$ 1,500 g) are at a heightened risk for developing growth restriction due to inadequate nutrition in the first weeks of life.[1–8] Despite advances in neonatal care, inadequate growth of VLBW infants remains very challenging. These challenges may arise from metabolic and gastrointestinal immaturity as well as from a compromised immune system and other medical complications.[9–11] If left untreated, growth deficiencies in the neonatal period have detrimental effects, such as growth failure and psychomotor deficits, that can persist throughout early childhood and into adulthood.[12–15]

Growth status and velocity are important health outcomes for VLBW infants.[16] The first 28 days of life, collectively considered the neonatal period, are especially important for growth and development because they represent the time that infants are most susceptible to illness and/or injury.[17,18] Therefore, regaining sufficient weight soon after birth is essential for establishing a consistent growth trajectory for the remainder of the infant's neonatal intensive care unit (NICU) stay. In fact, the American Academy of Pediatrics (AAP) committee on nutrition has recognized the importance of early, adequate nutrition for preterm infants and recommends that weight gain during NICU hospitalization should attempt to replicate the intrauterine growth velocity (15 g/kg/d) of a fetus at an equivalent gestational age (GA).[19] However, VLBW infants are often unable to attain such

intrauterine-like growth velocities due to physiological immaturity and the presence of comorbidities.

Aside from having a VLBW, the maternally deprived conditions inside the incubator do not provide the preterm infant with an optimal environment to mature and develop. One way of optimizing the NICU incubator may be to attempt to restore the maternal aspects of the intrauterine environment by providing the infant with his or her mother's voice and heartbeat sounds that were otherwise present in the womb. Previous studies have yielded important information regarding the potent effect of soothing sounds on a wide range of short-term outcomes, including improved oxygen saturation,[20] cardiorespiratory stability,[21] and behavioral states[22–24] as well as improved energy expenditure,[25] caloric intake,[26] weight gain,[23,27] feeding tolerance,[28] and feeding length.[29,30] However, the previous research limits our ability to attain solid conclusions regarding the effects of soothing sounds on neonatal growth for two main reasons. First, with the exception of one study,[26] most studies have focused on healthy preterm infants who are > 30 weeks' postmenstrual age,[25,29,30] rather than on VLBW infants in the first few weeks of life. Second, in most studies, infants were only briefly exposed to soothing sounds, usually for 2 to 3 days,[23,25,26] leaving the prolonged effects of auditory sounds on growth velocity outcomes largely unstudied. The present study aimed to fill this scientific void by (1) examining a high-risk population of VLBW infants born < 33 weeks' GA; (2) focusing on the first 28 days of life; and (3) using attenuated recordings of the infant's mother's voice and heartbeat designed to mimic the womb environment. Thus, the main purpose of this study was to provide VLBW infants with biological maternal sounds (BMS) and measure the effects on weight gain velocity during the neonatal period. It was hypothesized that infants exposed

to BMS during their NICU stay would have a faster weight gain velocity compared to retrospective matched controls.

## Study Design

### Participants

A total of 32 VLBW infants took part in this study. All subjects were admitted to the Brigham and Women's Hospital (BWH) NICU in Boston, Massachusetts. A prospective cohort of VLBW infants exposed to BMS during their NICU hospitalization were compared with a cohort of retrospective controls matched 1:1 for sex, birth weight (BW), GA, scores for neonatal acute physiology and perinatal extension (SNAPPE - II). The SNAPPE-II is a measurement of illness severity and mortality risk developed to predict in-hospital mortality based on nine different physiological criteria scored within the first 12 hours of life.[31] When there were two possible matches for an infant, the infant with the closest SNAPPE-II score, sex, GA, and BW was used as the match.

Inclusion criteria included the following: GA $\geq$ 25 and $\leq$ 33 weeks, as assessed by mother's dates and/or with the Ballard GA assessment; BW $\geq$ 700 g and $\leq$ 1,500 g. The age limits were chosen based on the knowledge that the human fetus begins to perceive and react to auditory information starting at approximately the 25th week of life[32,33] Exclusion criteria included the following: major chromosomal or congenital anomalies, major congenital infections, $\geq$ grade II intraventricular hemorrhage, necrotizing enterocolitis, and surgeries within the first 28 days of life.

The BMS group included 16 preterm infants (5 males, 11 females), with a mean birth GA of 28.8 weeks (standard deviation [SD] $\pm$ 2.2), mean BW of 1,089 g (SD $\pm$ 260), and SNAPPE-II score of 16.31 (SD $\pm$ 17.81). The retrospective

**Table 1** Clinical characteristics of study population

| Parameters | BMS | Matched control | p value[a] |
|---|---|---|---|
| Neonatal data | | | |
| Males, n (%) | 5 (31) | 5 (31) | 1.00 |
| Birth GA (wk) | 28.8 ± 2.2 | 28.9 ± 2.3 | 0.75 |
| Birth weight (g) | 1,089 ± 260 | 1,101 ± 231 | 0.45 |
| SNAPPE-II score | 16.31 ± 17.81 | 14.50 ± 16.46 | 0.24 |
| Antenatal corticosteroids, n (%) | 12 (75) | 15 (94) | 0.38 |
| Days to regain birth weight | 8.00 ± 4.13 | 7.31 ± 3.88 | 0.63 |
| Morbidities | | | |
| Sepsis, n (%) | 2 (13) | 2 (13) | 1.00 |
| PDA, n (%) | 8 (50) | 5 (31) | 0.38 |
| RDS, n (%) | 15 (94) | 14 (88) | 0.77 |
| CLD, n (%) | 10 (63) | 8 (50) | 0.56 |
| IVH (grade II), n (%) | 2 (13) | 3 (19) | 0.78 |

Abbreviations: BMS, biological maternal sounds; CLD, chronic lung disease; GA, gestational age; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; scores for neonatal acute physiology and perinatal SNAPPE-II.
Note: Morbidities are based on the first 28 days of life. Unless otherwise specified numbers are given as mean (± standard deviation).
[a]p value is a result of a paired t test or Mann-Whitney for comparisons between groups.

matched controls included 16 preterm infants (5 males, 11 females), with a mean birth GA of 28.9 weeks (SD ± 2.3), mean BW of 1,101 g (SD ± 231), and SNAPPE-II score of 14.50 (SD ± 16.46). The mean GA, BW, and SNAPPE-II scores between the groups were not significantly different (see ►**Table 1**). Further analysis of matching accuracy for each matched pair separately indicates an average difference of 56 g for BW, 3 days for birth GA, and 3.5 points for SNAPPE-II scores. In addition, there were no statistically significant differences between the groups on common neonatal morbidities including sepsis, respiratory distress syndrome, chronic lung disease (CLD), and intraventricular hemorrhage (see ►**Table 1**).

## Biological Maternal Sounds Group

### BMS Recording

BMS recording was performed in a specialized recording studio at BWH. Voice recordings were acquired using a large-diaphragm condenser microphone (KSM44, Shure, Niles, IL) that captured a wide range of maternal vocalizations, such as speaking, reading, and singing. Heartbeat recordings were acquired with a digital stethoscope (ds32a, Thinklabs Digital Stethoscopes, Centennial, CO). Next, sound recordings were attenuated using a low-pass filter with a cutoff of 400 Hz to allow the highest fidelity of biological sound reproduction. The recorded soundtrack was then mixed with soothing sounds and uploaded onto an MP3 player (Philips Electronics, SA2RGA04KS, Amsterdam, The Netherlands) for playback inside the infant's isolette/crib $4 \times$ per 24-hour period for 45 minutes.

### Sound Safety

The audio system used in this study has been previously validated in a safety and feasibility study from our laboratory.[34] This particular system has been shown to: (1) have no electrical interference with medical equipment, such as cardiac monitors and ventilators; (2) withstand the high temperature (about 36°C) and humidity (approximately 75%) levels often present inside the isolette; (3) be robust against frequent cleaning with disinfectant as per the infection control guidelines; and (4) deliver maternal sounds at a safe, fixed decibel level. Loud peaks of maternal vocalization ($< 65$ decibel A-weighted (dBA)) were attenuated to achieve a safe level of sound delivery equivalent to normal human conversation.

### Implementation of BMS in the NICU

Implementation of BMS into routine NICU practices was made possible by an effective collaboration between researchers and NICU medical staff, especially the nurses. Nurses were instructed to provide BMS $4 \times$ per 24-hour period by pressing the "play" button on the MP3 player located behind the infant's isolette/crib. Implementation of BMS was documented daily by the bedside nurse.

## Control Group

Infants in the control group received standard NICU care without implementation of BMS. This retrospective cohort of infants included neonates who were admitted to the BWH NICU within 3 years from the study onset. No changes in NICU construction, medical equipment, or nutritional protocols were made during this time.

### Data Collection

Patient data were collected from medical records and nursing flow sheets. Data included BW, GA, sex, birth head circumference, administration of antenatal corticosteroids, and SNAPPE-II scores. A 28-day growth trajectory was used to examine the average daily weight gain (g) across the two groups during the neonatal period. To examine the weight gain velocity two common methods described in the literature were computed.

### Calculating Growth Velocity

Weight gain velocity (g/kg/d) was determined by taking the infant's daily weight gain (g) divided by the previous day's weight (kg) for the first 28 days.

The exponential model (EM) is based on the premise that growth in biological systems is often nonlinear and occurs at a fraction of the previous weight. The EM accurately estimates postnatal growth velocity in VLBW infants throughout the NICU stay.[35–39] The equation used to calculate EM is: estimated $GV = [1,000 \times \mathrm{Ln}\,(Wn/W1)]/(Dn - D1)$, where $GV$ = growth velocity, $W$ = weight in grams, $D$ = day, $1$ = beginning of time interval, and $n$ = end of time interval in days.

Additional outcome measures included the days to regain BW, duration of no feeding by mouth, days until full enteral feeds (140 mL/kg/d), caloric intake, and total fluid intake (mL/kg/d).

### Statistical Analysis

The nutritional outcomes are presented in ►**Table 2**. A paired $t$ test was used to examine the 28-day growth trajectory between the two groups. A linear mixed model (SPSS version 20) was used to examine the effect of the dependent variable (weight gain velocity) between the two groups (BMS versus matched control). Covariates included in the model were chosen a priori on the basis of their clinical relevance to impact growth during the neonatal period and included: birth GA, CLD, and the days to regain BW.[40,41] These covariates were entered into the model to account for differences in these factors thereby further increasing the power to detect significant effects.

## Results

The 28-day growth trajectory reveals that, on average, infants exposed to BMS gained significantly more weight ($1,220 \pm 159$ g) compared with matched controls ($1,204 \pm 137$ g; $t = 3.35$, $p = 0.002$; see ►**Fig. 1**). Significant effects were also evident in growth velocity. A paired $t$ test revealed a significant difference between infants exposed to BMS versus matched controls ($t = 2.21$, $p = 0.043$) with an average growth velocity of 13.13 g/kg/d (SD ± 3.17) and 10.96 g/kg/d (SD ± 2.54), respectively (►**Table 2**). Statistical significance remained strong after entering the growth velocity data into a linear mixed model (fixed effects) using birth GA, CLD, and the days to regain BW as covariates ($t = 4.26$, $p < 0.001$)

**Table 2** Nutritional outcomes

| Outcomes | BMS (n = 16) | Matched-control (n = 16) | p-value |
|---|---|---|---|
| | Linear mixed model estimated means[a] | | |
| Weight Gain Velocity is (g/kg/day) | 13.45 (±7.37) | 10.65 (±7.37) | p < .001 |
| | Paired t-test means | | |
| Weight Gain Velocity (g/kg/day) | 13.13 (±3.17) | 10.97 (±2.54) | p = .025 |
| 28-day Growth Trajectory (g) | 1,220 (±159) | 1,204 (±137) | p = .002 |
| Duration NPO (days) | 2.56 (±2.70) | 4.13 (±4.35) | p = .18 |
| Full enteral feeds (140 ml/kg/day) | 14.43 (±7.50) | 15.25 (±9.09) | p = .51 |
| Total Fluid Intake (ml/kg/day) | 138.14 (±3.55) | 138.38 (±10.41) | p = .93 |
| Caloric Intake (kcal/kg/day) | 100.75 (±14.32) | 99.24 (±15.25) | p = .73 |

Abbreviation: BMS, biological maternal sounds; NPO, no oral feeding.
Note: Numbers are given as mean (± standard deviation).
[a]Estimated means have been entered into a linear mixed model to account for the following covariates: gestational age, chroniclung disease, days to regain birth weight.

with an average growth velocity of for the BMS group of 13.45 g/kg/d (SD ± 7.37) and 10.65 g/kg/d (SD ± 7.37) for the control group (►Table 2).

A paired t test estimating postnatal growth velocity based on the EM (see Methods) revealed that the BMS infants (12.54 ± 3.22 g/kg/d) had a faster growth velocity compared with control infants (10.37 ± 2.72 g/kg/d; t = 2.20, p = 0.044). Overall, it is clear that BMS positively influences weight gain in the first 28 days of life.

There were no significant group differences on days to regain BW (p = 0.63), duration of no feeding by mouth (p = 0.18), days until full enteral feeds (p = 0.51), total fluid intake (p = 0.93), or caloric intake (p = 0.73; see ►Table 2).

## Discussion

This study examined the effects of BMS on weight gain velocity in VLBW infants during the first 28 days of life. The results suggest that daily exposure to mother's voice and heartbeat



**Fig. 1** The 28-day growth trajectory for the BMS group (red) compared to the control group (blue). Green vertical arrow indicates the average day of life when infants in the BMS group were first exposed to maternal sounds. An improvement in weight gain was evident at approximately day of life 13 when the BMS infants surpassed the controls. Abbreviation: BMS, biological maternal sounds.

sounds while in the incubator can result in a significantly faster weight gain velocity compared with routine exposure to NICU sounds. These effects remained strong after controlling for possible covariates, including GA, CLD, and days to regain BW. Infants receiving BMS gained an average of 13.13 g/kg/d—that is 2.16 g/kg/d more than the control infants (10.97 g/kg/d), and closer to the AAP recommendation of 15 g/kg/d. Although the weight gain increase may seem small on a day-to-day basis, over time it leads to meaningful differences. For instance, at day of life 28 infants in the BMS group weighed on average 1,532 g and infants in the matched-control group weighed on average 1,470 g. Although these amounts are not substantial for a full-term infant, considering the small size and the initial starting point of these VLBW infants, any additional weight gain is significant.

### Nutritional Outcomes

Interestingly, our data show that the primary difference between the groups was in weight gain velocity (p < 0.001; linear mixed model). However, despite emerging trends, no significant group differences were found for the other related nutritional outcomes, such as days without oral feeding, days to full enteral feed, total fluid intake, and days to regain BW (see ►Table 2). For example, the BMS infants reached full enteral feeds slightly sooner (14.43 days) compared to the control infants (15.25 days). Further research is needed to confirm whether BMS reduces time to full enteral feeding. Improvements in environment have been shown to reduce the days to reach full enteral feeds. Erickson and colleagues found that the time to reach full enteral feeds was reduced in infants in a private suite room compared with infants in an open-bay NICU.[42] Therefore, it is possible that the BMS group had a maternally enhanced NICU environment that fostered growth and reduced the time to reach full enteral feeds.

### Several Possible Mechanisms for Increase in Growth Velocity

The lack of significant differences between the groups on days NPO, days to full enteral feed, and total fluid intake leave us to
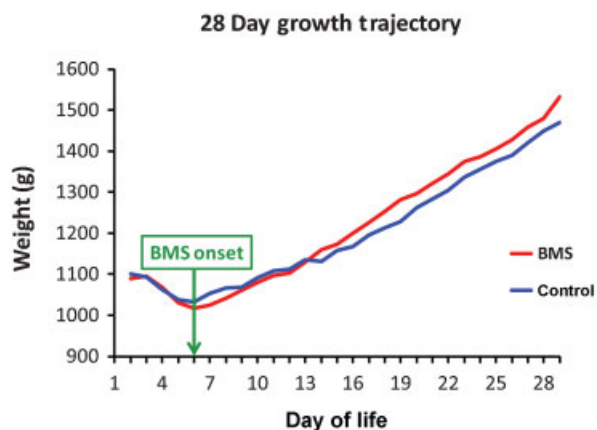
assume that the BMS infants might have managed to preserve more energy, which in turn contributed to their improved weight gain. Although we did not measure this directly, we can only speculate that the soothing effects of BMS led to an overall reduction in stress; this led to improved sleep-wake cycles and behavioral states, which all together helped the infant to preserve more energy, thereby improving weight gain. Several possible mechanisms may be considered.

The inability of the premature infant to adapt accordingly from the soothing womb environment to the overwhelming NICU environment can result in an immense amount of stress that can impinge on growth and development.[43–46] Previous research has shown that the accumulation of background noise in the NICU may result in detrimental health effects.[47–51] Controlling the environment may allow for energy conservation and may, in turn, result in appropriate growth and development.[44] It is possible that the BMS replaced the noxious NICU noise with meaningful maternal stimulation resulting in an improved environment, thereby reducing the infant's stress level. However, in the absence of more solid physiological evidence for stress levels (e.g., cortisol), this hypothesis remains a rather speculative explanation.

Another possible explanation for the increase in weight gain observed by infants in the BMS group might be due to improved behavioral states. Previous studies have provided live music to premature infants in the NICU and found improved behavioral scores in the 30-minute interval after the music had been played.[22] Another study found a trend toward more mature sleep-wake cycles in subjects who were exposed to music compared with controls, suggesting that there might be a small effect of music on quiet sleep in newborns.[52] Thus, it is possible that infants receiving BMS were in active states longer and acquired more quiet sleep, which in turn helped them to preserve more energy and increase their daily weight gain. A subsequent study using a larger randomized controlled trial needs to be completed to further examine this hypothesis in more detail.

### Weight Gain and Neurodevelopment

Growth status and velocity are important markers of health and well-being in VLBW infants. The benefit of early weight gain can extend beyond the neonatal period as postnatal growth in premature infants is a strong predictor of concurrent morbidities and neurodevelopmental outcomes.[2,3,53–55] Ehrenkranz and colleagues found that as the rate of weight gain and head circumference increased, the incidence of cerebral palsy, mental developmental index, psychomotor developmental index scores < 70, abnormal neurological examination, and neurodevelopmental impairment fell.[41] Therefore therapies, like BMS, that can noninvasively improve weight gain may possibly correlate with improved long-term neurodevelopmental outcomes in VLBW infants.

### Study Limitations

This was an exploratory study and the generalization of the results may therefore be limited. The relatively small sample size was due to the investigators' goal of ensuring clinically relevant outcomes prior to pursuing a larger, randomized controlled trial. In addition, the small sample size was a result of our selective recruitment of a homogeneous cohort of VLBW infants, ruling out those who did not have morbidities that could potentially account for changes in weight gain velocity other than BMS.[56] However, these inclusion criteria significantly limited our sample size as it was difficult to find VLBW infants who did not have such comorbidities. The small sample size tested is a possible limitation to this study.

An additional potential limitation of the present study is our inability to determine the effects of BMS beyond the neonatal period. For example, it would have been interesting and clinically relevant to examine whether daily exposure to mother's voice and heartbeat can influence the infants' weight at NICU discharge. This, however, was not feasible for this specific study cohort because many of the infants were transferred to another NICU in a community hospital closer to home, leaving us with no data on their weight gain at term-equivalent age.

## Conclusion

Exposure to biological maternal sounds during NICU hospitalization may improve weight gain velocity in VLBW infants in the first 28 days of life. These promising results require further studies with a larger sample size to confirm the findings and to elucidate the underlying mechanisms.

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